D7

PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : A61K 31/19, 31/20 — A1

(11) International Publication Number: **WO 99/58120**

(43) International Publication Date: 18 November 1999 (18.11.99)

(21) International Application Number: PCT/NO98/00143

(22) International Filing Date: 8 May 1998 (08.05.98)

(71)(72) Applicant and Inventor: BERGE, Rolf [NO/NO]; Tjørnhaugen 50, N–5062 Bønes (NO).

(74) Agent: A/S BERGEN PATENTKONTOR; Strandgt. 191, N–5004 Bergen (NO).

(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published
With international search report.

(54) Title: USE OF NON–β–OXIDIZABLE FATTY ACID ANALOGUES FOR TREATMENT OF SYNDROME–X CONDITIONS

(57) Abstract

There is disclosed a use of non–β–oxidizable fatty acid analogues of the general formula (I): Alkyl–X–CH_2COOR, wherein alkyl represents a saturated or unsaturated hydrocarbon group of from 8–22 carbon atoms, X represents O, S, SO, SO_2, and Se, and R represents hydrogen or C_1–C_4 alkyl, for the preparation of a pharmaceutical composition for the treatment and/or prevention of Syndrome–X conditions, with the exception of the Syndrome–X conditions claimed in European patent applicaiton 345.038 and International patent application WO 97/003663. There is also disclosed a method for the treatment and/or for prevention of the Syndrome–X conditions.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece			TR	Turkey
BG	Bulgaria	HU	Hungary	ML	Mali	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MN	Mongolia	UA	Ukraine
BR	Brazil	IL	Israel	MR	Mauritania	UG	Uganda
BY	Belarus	IS	Iceland	MW	Malawi	US	United States of America
CA	Canada	IT	Italy	MX	Mexico	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NE	Niger	VN	Viet Nam
CG	Congo	KE	Kenya	NL	Netherlands	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NO	Norway	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	NZ	New Zealand		
CM	Cameroon			PL	Poland		
CN	China	KR	Republic of Korea	PT	Portugal		
CU	Cuba	KZ	Kazakstan	RO	Romania		
CZ	Czech Republic	LC	Saint Lucia	RU	Russian Federation		
DE	Germany	LI	Liechtenstein	SD	Sudan		
DK	Denmark	LK	Sri Lanka	SE	Sweden		
EE	Estonia	LR	Liberia	SG	Singapore		

USE OF NON-ß-OXIDIZABLE FATTY ACID ANALOGUES FOR TREATMENT OF SYNDROME-X CONDITIONS.

The invention relates to 3-substituted fatty acids acting on PPAR receptors, and a new way to prevent and treat the syndrome-X disease, a term to express the link between NIDDM, obesity, atherosclerosis, hypertension and premature cardiovascular disease, CD.

Hyperlipidemia and obesity afflict an increasing proportion of the population in Western societies and are associated with the development of serious conditions such as atherosclerosis, hypertension and insulin resistance. These conditions may eventually lead to the clinical manifestations of coronary heart diseases (CD) and non-insulin dependent diabetes mellitus (NIDDM). The link between NIDDM, atherosclerosis, hypertension and CD has been termed Syndrome-X, and elevated levels of plasma fatty acids appear to play a central role in the development of this class of diseases. More closely the term Syndrome X is inter alial related to conditions of low levels of high density lipoprotein-cholesterol (HDL-C), high levels of low density lipoprotein-cholesterol (LDL-C), raised triglycerides, glucose intolerance, increased blood pressure and abdominal obesity and restinose.

Treatment with modified fatty acids represent a new way to treat these diseases.

Modified fatty acids reduce the degree of obesity and reduce the levels of plasma fatty acids. Secondly, they are

potent antidiabetic compounds that lower the hyperglycaemia and hyperinsulinemia observed in animal models of non-insulin dependent diabetes (NIDDM) and in human NIDDM. Thirdly, they promote adipocyte differentiation. Finally, they have an anti-atheriosclerotic potential by a) lowering blood, lipids, b) protect LDL against oxidation, c) and lowering of homocysteine.

Thus the present invention relates to the use of certain non-ß-oxidazable fatty acid analogues (3-substituted) for the manufacture of medicaments for patients with a variety of Syndrome X - conditions, namely low levels of high density lipoprotein-cholesterol (HDL-C), high levels of low density lipoprotein-cholesterol (LDL-C), raised triglycerides, glucose intolerance, increased blood pressure, NIDDM, abdominal obesity, and restinose.

The diseases to be treated may include obesity and non-insulin dependent diabetes mellitus (NIDDM), coronary heart diseases (CD), atherosclerosis, hypertension, and represents an improvement of existing therapy (omega 3-fatty acids, fibrates, statines and thiazolidinediones). Syndrome-X is also sometimes considered as a link between these individual diseases.

Fibrates, fatty acids and antidiabetic compounds such as thiazolidinediones exert their mode of actions via peroxisome proliferator- activated receptors (PPAR). Fibrates and fatty acids via the α receptors (PPAR-α) and thiazolidinediones are ligands for PPAR-γ. The non-β-oxidizable fatty acid analogues, however, have dual functions:

1) regulate intracellular metabolism including fatty acid catabolism and extracellular lipoprotein metabolism, and also by afflicting gene expression mediated via PPAR-α.
2) improve insulin sensitivity in insulin resistant subjects which is mediated via PPAR-γ and further emphasising the intricate network combining the regularly

circuits involved in adipocyte differentiation and fatty acid metabolism disorders as obesity and insulin resistance.

Thus, both liver and adipose tissue are important targets for the effect of non-ß-oxidizable fatty acids on fatty acid catabolism (PPAR-α) and insulin sensitivity (PPAR-γ), respectively.

In this connection reference is made to European Patent Specification No. 345.038 (NORSK HYDRO A.S., priority of GB-8813012 of June 1988) (patent I) and International Patent Application No. WO 97/03663, (patent II), which disclose the use of non-b-oxidizable fatty acid analogues of the general formula (I):

Alkyl-X-CH_2COOR

wherein alkyl represents a saturated or unsaturated hydrocarbon group of from 8-22 carbon atoms, X represents O, S, SO, and SO_2, Se and R represents hydrogen or C_1-C_4 alkyl, for the manufacture of a medicament for the treatment of hyperlipidaemic conditions and for reducing the concentration of cholesterol and triglycerides in the blood of mammals. The EP-specification also discloses the preparation of compounds of the actual non-ß-oxidizable fatty acid analogues wherein the substitute X represents O, S, SO, SO_2. The EP-specification reports that the compounds in question exhibit favourable lipid lowering effects in blood of mammals, such as rats, and possess low toxicity measured as increase in liver weight and increased paroxysmal ß-oxidation.

Further it has been found that analogues with the general formula alkyl-S-CH_2COOR and alkyl-Se-CH_2COOR functions as antioxidants and inhibit the LDL oxidative modifications. Thus, the antiatherosclerotic properties of these compounds are supposed to be related to their antioxidantic and hypolipidemic effects in blood of animals, i.e. by reducing the concentration of cholesterol and triglycerides.

It has now been found that the analogues of the above mentioned non-ß-oxidizable fatty acids, i.e, the 3-substituted fatty acid analogues have broader area of applications.

New strategies have been developed to search for compounds that both are ligands for PPAR-α (lipid-lowering effects and anti-obesity) and a ligand for PPARγ (insulin-sensitivity effect).

In feeding experiments with such fatty acid analogues, the results show that they are potent antidiabetic compounds that lower the hyperinsulinemia, hypertriglyceridemia and also reduce the body fat content in animal models of non-insulin dependent diabetes (NIDDM).

The compounds of the present invention probably act by enhancing the peripheral sensitivity to insulin. The fatty acids analogues upregulate the lipoprotein lipase LPL expression (LPL), which hydrolyses lipoprotein triglycerides. This upregulation is probably linked to activation of PPARγ. On the other hand, PPARγ is a key factor for adipocyte differentiation and these fatty acid analogues are efficient promoters of adipocyte differentiation in vitro.

The thiazolidinediones also promote adipocyte differentiation in vitro. Thus, it could be questioned whether a thiazolidinedione therapy aimed at improving insulin sensitivity would promote the recruitment of new adipocytes in vivo, an effect which could be deleterious since most of the NIDDM patients are already obese. In contrast to thiazolidinediones, the fatty acid analogues reduce adipose tissue accumulation in vivo.

The link between NIDDM, atherosclerosis, hypertension and coronary heart diseases has been termed syndrome X, and elevated levels of plasma fatty acids appears to play a central role in the development of this class of diseases. As 3-substituted fatty acids are ligands for PPAR-α and thereby involved in fatty acids catabolism by increasing the fatty acid oxidation, a 3-substituted fatty acid therapy will increase the diversion of fatty acids to

mitochondrial ß-oxidation and increase the rate of transfer of fatty acids from the serum compartment into hepatocytes giving a net reduction of the non-esterified fatty acid (NEFA) levels in plasma.

Accordingly the present invention relates to the use of non-ß-oxidizable fatty acid analogues of the general formula (I):

Alkyl-X-CH_2COOR

wherein alkyl represents a saturated or unsaturated hydrocarbon group of from 8-22 carbon atoms, X represents O, S, SO, SO_2, and Se, and R represents hydrogen or C_1-C_4 alkyl, for the preparation of a pharmaceutical composition for the treatment and/or for prevention of Syndrome-X conditions, with the exception of the Syndrome-X conditions claimed in European patent application 345.038 and International patent application WO 97/003663.

According to a preferred embodiment, a pharmaceutical composition is prepared for the treatment and/or for prevention of conditions of low levels of high density lipoprotein-cholesterol (HDL-C), raised triglycerides, glucose intolerance, increased blood pressure (hypertension) and abdominal obesity, NIDDM and restinose.

According to a preferred embodiment, use is made of a pharmaceutical composition wherein the compound of formula (I) is tetradecylthioacetic acid, or tetradecylseleoacetic acid.

According to another aspect, the invention relates to a method for the treatment and/or for prevention of Syndrome-X conditions, with the exception of the Syndrome-X conditions claimed in European patent application 345.038 and International patent application WO 97/003663, said method comprising administering to a mammal in need thereof, an effective amount of a non-ß-oxidizable fatty acid analogues of the general formula (I):

Alkyl-X-CH_2COOR

wherein alkyl represents a saturated or unsaturated hydrocarbon group of from 8-22 carbon atoms, X represents O, S, SO, SO_2, and Se, and R represents hydrogen or C_1-C_4 alkyl.

More specific there is disclosed a method for the preparation of a pharmaceutical composition for the treatment and/or for prevention of:

- metabolic conditions of low levels of high density lipoprotein-cholesterol (HDL-C), and/or high levels of low density lipoprotein-cholesterol (LDL-C).
- raised triglycerides,
- glucose intolerance,
- increased blood pressure,
- NIDDM,
- restinose, and/or
- abdominal obesity.

Preferably, according to the method, the compound of formula (I) is tetradecylthioacetic acid, or the compound of formula (I) is tetradecylselenocetic acid, or in the compound of formula I, X is Oxygen (O), Sulfur-I-oxide (SO) or Sulfurdioxide (SO_2).

RESTENOSIS.

THE RESTENOSIS AFTER PERCUTANEOUS TRANSLUMINAL CORONARY ANGIOPLASTY (PTCA).

The compounds specified according to the present invention are also suitable for the treatment of restenosis. Restenosis remains a major problem limiting the long-term success of catheter based balloon interventions in the coronary arteries and in the main arteries of the head, kidneys and lower limbs. Restenosis occurs between 1-6 months after the intervention. The mechanism involves proliferation of smooth muscle and hyperplasia of the endothelium which results in narrowing of the arteries in the same site as the original balloon dilatation. There are two mechanisms by which restenosis may be reduced, either via reduced thickening of the vessel wall or by remodell-

ing. Remodelling is when the vessel changes shape, the lumen diameter increases and the net effect is a dilatation of the vessel.

It has now been found that the tetradecylthioacetic acid (i.e. the fatty acid, 3-THIA-) probably via its anti-oxidant properties influences favourably the remodelling of the vessel wall, while the arterial wall thickening is un-affected. We assume that the quite similar selen containing fatty acid will exert the same properties, and also at the same time is more potent in its action.

OBESITY

Obesity is an important medical problem leading to high blood pressure, heart failure, diabetes, and myo-cardial infarction. Weight reduction with various diets have a high recurrence rate, and drug therapy has been limited mainly due to severe side effects. Compound I has weight reducing properties by its actions on adipose tissue. Thus, the non-ß-oxidizable fatty acid analogues may also be used for the manufacture of a weight reducing slimming-product for persons who wish to go through a slimming program.

The present invention provides fatty acid analogues to be potent antidiabetic compounds that can lower hyper-glycaemia, hyperinsulinemia, hypertriglyceridmia, hyper-cholesterolemia and to reduce obesity, reduce susceptibili-ty to LDL oxidation in human NIDDM.

The compounds used according to the present invention wherein the substituent **X** is a sulphur atom or selenium atom may be prepared according to the following general procedure:

X is a sulphur atom:

The thio-substituted compound used according to the present invention may be prepared by the general procedure indicated below:

$$\text{Alkyl-Hal} + \text{HS-CH}_2\text{COOR} \xrightarrow{\text{Base}} \text{Alkyl-S-CH}_2\text{-COOR}$$

The sulphur-compound, namely, etradecylthioaceticacid, $(CH_3-(CH_2)_{13}-S-CH_2-COOH$ was prepared as shown in EP-345.038, page 3, last paragraph.

X is a selenium atom:

the seleno-substituted compound used according to the present invention may be prepared by the following general procedure

1. $\text{Alkyl-Hal} + \text{KSeCN} \Rightarrow \text{Alkyl-SeCN}...$
2. $\text{Alkyl-SeCN} + BH_4^- \Rightarrow \text{Alkyl-Se}^-$
3. $\text{Alkyl-Se}^- + O_2 \Rightarrow \text{Alkyl-Se-Se-Alkyl}$

This compound is purified by carefully crystallisation from ethanol or methanol.

4. $\text{Alkyl-Se-Se-Alkyl} \xrightarrow{BH_4^-} 2\ \text{Alkyl-Se}^-$
5. $\text{Alkyl-Se}^- + \text{Hal-CH}_2\text{-COOH} \Rightarrow \text{Alkyl-Se-CH}_2\text{ - COOH}$

The final compound, e.g. when alkyl is tetradecyl, $(CH_3-(CH_2)_{13}-Se-CH_2-COOH$ can be purified by crystallisation from diethyl ether and hexane. This product may be fully characterized by NMR, IR and molecular weight determination.

The methods for the synthesis and isolation of these Sulphur and Selenium compounds, and the compound wherein X of formula I is Oxygen (O), Sulphur-I-oxide (SO) and Sulphurdioxide (SO_2) are disclosed in the abovementioned

European Patent Specification No. 345.038 (patent I) and International Patent Application No. WO 97/03663, (patent II).

EXPERIMENTS

EXPERIMENT 1

Hypolipidemic effect

Male obese Zucker fa/fa rats, weighing 100 g at the start of the experiment, were housed in pairs in metal wire cages in a room maintained at 12 h light-dark cycles and a constant temperature of 20±3 °C. The animals were acclimatised for at least one week under these conditions before the start of the experiment.

Compound I (tetradecylthioacetic acid) prepared in accordance with procedure described previously, and palmitic acid (control), was suspended in 0.5% (w/v) carboxymethyl cellulose (CMC). Six animals were used in both groups. Compound I (tetradecylthioacetic acid) and palmitic acid were administered at a dose of 300 mg/ day/ kg body weight, by gastric intubation (gavage) once daily for 10 days. The rats were fasted for 2 hours before termination of the experiment. Blood and organs were collected. Very low density lipoproteins (VLDL) were prepared by sequential ultracentrifugation. Lipid concentrations in plasma and very low density lipoproteins (VLDL) were determined using an autoanalyzer. Results obtained are reported in Table 1.

TABLE 1.

Effect of Compound I (tetradecylthioacetic acid) on lipid levels in obese Zucker fa/fa rats.

	Decreased lipid level in plasma (% of control)		
	Triglycerides	Cholesterol	Phospholipides
Compound I	72	73	71

Decreased lipid level in VLDL (% of control)			
	Triglycerides	Cholesterol	Phospholipides
Compound I	63	115	88

Table 1 shows that Compound I (tetradecylthioacetic acid), exhibits a good hypolipidemic effect in blood of obese Zucker fa/ fa rats. A sub-chronic toxicity study has been performed in dog by Corning Hazleton, Europe. The compound possesses low toxicity. Compound I (tetradecylthioacetic acid) are therefore potentially useful as a medical compound in this respect.

Hypoglycaemia and increased insulin sensitivity

The effect of tetradecylthioacetic acid (Compound I) on the plasma levels of insulin and glucose.

TABLE 2

Effect of Compound I (tetradecylthioacetic acid) on insulin and glucose levels in obese Zucker fa/fa rats.

Decreased levels of insulin in plasma after 10 days of treatment (% of control)		
	Insulin	Glucose
Compound I	60	90

These results show that the tetradecylthioacetic acid affects the insulin and glucose levels in obese Zucker fa/fa rats.

The results also suggest that Compound I (tetradecyl-thioacetic acid) increases the insulin sensitivity and glucose tolerance in obese Zucker fa/fa rats. The body weight and weight gain was not altered in the treated rats, compared to controls.

TABLE 3

Effect of Compound I (tetradecylthioacetic acid) on g epidydimal fat / g body weight in Zucker fa/fa rats.

Decreased levels of epidydimal fat after 10 days of treatment(g epidydimal fat/g body weight	
Control	Compound I
0,0044 ±0,0001	0,0039 ±0,0001

The amount (or ratio of) epidydimal fat/body weight however decreased slightly but significant during the treatment (table 3). When obese Zucker fa/ fa rats are treated with the thiazolidinedione or pioglitazone, which lower hyperglycaemia and hyperinsulinemia, there is a marked increase in weight gain during the treatment. Table 4 shows that Compound I (tetradecylthioacetic acid) significantly increases the activity of LPL. Also mRNA levels of LPL increased (data not shown).

Experiment.

A. Male Wistar rats were treated with compound 1 for 7 days. Total RNA was isolated from epidydimal adipose tissue and electrophoresis followed by northern blotting was performed. The blot was hybridised with LPL cDNA. The results are illustrated in the accompanying Figure 1. This figure shows that the mRNA of LPL in epidymal adipose tissue is increased in normal male Wistar rats after 1 week of treatment with compound 1.

B. The mouse preadipocyte cell line, 3T3-L1 (ATCC), was maintained in Dulbecco's modified Eagle's minimal essential medium and supplemented with 10% dilapidated and charcoal-treated fetal calf serum, L-glutamine and antibiotics. Compound 1 was solved in ethanol and added to the medium at a concentration of 100 mM. Control cells received ethanol

only. Northern-blotting with total RNA was performed and the filters were hybridised using human LPL cDNA. The results are illustrated in the accompanying Figure 2. This figure shows that compound 1 induce adipocyte differentiation measured by the appearance of LPL mRNA levels in 3T3-L1 cells.

TABLE 4.

Effect of Compound I (tetradecylthioacetic acid) on LPL activity in inguinal adipose tissue in Zucker fa/fa rats.

LPC activity (g epidydimal fat/ g body weight)	
Control	Compound I
91 ± 13	137 ± 6

Figure 1 panel A, shows that the mRNA levels of LPL in epidydimal adipose tissue is increased after 1 week of treatment with compound 1 in normal male Wistar rats. Panel B shows that compound 1 induce adipocyte differentiation measured by the appearance of LPL mRNA levels in 3T3-L1 cells.

Antioxidant effect

Male obese Zucker fa/fa rats, weighing 100 g at the start of the experiment, were housed in pairs in metal wire cages in a room maintained at 12 h light-dark cycles and a constant temperature of 20±3 °C. The animals were acclimatised for at least one week under these conditions before the start of the experiment.

Compound I (tetradecylthioacetic acid) prepared in accordance with the procedures disclosed above, and palmitic acid (control), was suspended in 0.5% (w/v) carboxymethyl cellulose (CMC). Six animals were used in both groups. Compound

I (tetradecylthioacetic acid) and palmitic acid were administered at a dose of 300 mg/ day/ kg body weight, by gastric intubation (gavage) once daily for 10 days. The rats were fasted for 2 hours before termination of the experiment. Blood and organs were collected. Homocystein levels were determined using an autoanalyzer. The homocystein level was reduced 45% compared to control. Total lipids were extracted from liver and plasma. The lipids were evaporated, saponified and esterified prior to separation using a Carlo Erba 2900 gas-chromatograph.

Table 5

Effect of Compound I (tetradecylthioacetic acid) on fatty acid composition in obese Zucker fa/fa rats.

Fatty acid composition in liver (% of total)		
	Oleic acid	Monounsaturated tetradecylthioacetic acid
Control	9.9 ± 1.4	0.0
Compound I	14.9 ± 1.0	1.1 ± 0.2
Fatty acid composition in plasma (% of total)		
	Oleic acid	Monounsaturated tetradecylthioacetic acid
Control	18.3 ± 0.9	0.0
Compound I	22.1 ± 0.5	0.2 ± 0.1

Table 5 shows that oral administration of compound I (tetradecylthioacetic acid) increases the level of oleic acid in both liver and plasma. Also a delta-9-desaturated product of tetradecylthioacetic acid accumulated in both plasma and liver.

RESTINOSIS Experimental methods:

3-THIA was administered to pig coronary arteries by local drug delivery via a special angioplasty balloon catheter with side holes in the balloon. Coronary balloon angioplasty injury to the vessel wall was performed to the LAD or Cx using an oversized balloon, thereafter the substance 3-THIA (tetradecylthioacetic acid) was infused via the balloon with side holes. Twenty minipigs were randomised to this treatment or infusion of placebo using the same technique. Radiolabelled 3-THIA was also infused into 2 extra pigs in which presence of the radioactive substance was confirmed after 4-6 weeks. The luminal diameter of coronary arteries was measured in control pigs (placebo group) and pigs treated with compound I.

TABLE 6

The luminal diameter of coronary arteries in the placebo and compound I pigs.

	Diameter (mm)	
	Placebo	Treated with Compound I
Before injury	2,7	2,6 NS
Follow up (after 6 weeks)	2,2	1,3 ($p<0,001$)

*NS = not significant

Results:

The luminal diameter at angiographic and ultra sound follow-up at 4 weeks was significantly smaller in the placebo group than in the active treatment group with 3-THIA (tetradecylthioacetic acid). Histology showed no difference in wall thickening between the two groups. We conclude that local application of the antioxidant agent tetradecylthioacetic acid alters vessel remodelling rather

than intimal hyperplasia after balloon angioplasty.

In another experiment rabbits were treated orally with a medicament containing the 3-THIA-compound (tetradecylthioacetic acid) before and after balloon angioplasty of the iliac arteries. The same results were found showing that remodelling was favourably influenced with open arteries in the group of rabbits treated with active compound, and in stenosed arteries in the placebo group (by angiography) at follow-up.

We conclude from these studies that a medicament containing the 3-THIA-compound reduces restenosis. This was judged by angiography after balloon angioplasty, administered either orally or locally. The effect is the same in coronary and peripheral arteries.

OBESITY. Experiments.

2 groups of 6 male Wistar Rats were randomly selected, and studied for weight development over a period of 12 week. The body weight of each wistar rat was measured at the start of the experiment. All animals in both groups received individually the same amount of food (nutrition) during the experimental period of 12 weeks. All animals in one of the groups were orally administrated with the medicament comprising tetradecylthioacetic acid (compound I). The other group was the control group. After the 12 week period the body weight of rats were measured again. The results of the experiment are shown in the following table.

Table 7.

Effect of compound I (tetradecylthioacetic acid) on body weight of male Wistar rats after 12 weeks of treatment.

	Body weight gain
control (rats not treated with compound I)	293 ± 27
Compound I	234 ± 20 (p<0,05)

The results show that oral administration of tetradecylthioacetic acid leads to significant weight loss in obese individuals with concomitant medical conditions (examples: heart disease and hypertension), and induces weight loss in obese individuals which are otherwise healthy. Said effects are assumed to be similar when the sulphur-compound is exchanged with the selenium compound, i.e. tetradecyl-seleno-acetic acid, and with oxygen O, SO and SO_2 as mentioned above.

The compounds used according to the present invention may be administered to patients suffering from non-insulin dependent diabetes mellitus, coronary heart diseases and obesity. Alternatively by dietary they may prevent the disease.

The dosage range for the compounds according to the present application is contemplated to be from 5 to 100 mg/day for the average adult patient. Of course, the actual dose necessary will depend on the patient's condition and will have to be determined by the attending physical from case-to-case.

For oral pharmacological compositions such carrier material as, for example, water, gelatine, gums, lactose, starches, magnesium-stearate, talc, oils, polyalkene glycol, petroleum jelly and the like may be used. Such pharmaceutical preparation may be in unit dosage form and may additionally contain other therapeutically valuable

substances or conventional pharmaceutical adjuvants such as preservatives, stabilising agents, emulsifiers, buffers and the like. The pharmaceutical preparations may be in conventional liquid forms such as tablets, capsules, dragees and the like, in conventional dosage forms, such as dry ampulles, and as suppositories and the like.

For parenteral administration the compounds according to the present invention may be administered as solutions, suspensions or emulsions using conventional pharmaceutical carrier materials such for example water for injection, oils, polyalkylene glycols and the like. These pharmaceutical preparations may further include conventional pharmaceutical adjuvants, such as preservatives, stabilising agents, emulsiers, salts for the adjustment of the osmotic pressure, buffers and the like. The preparations may also contain other therapeutically active materials.

C L A I M S.

1. Use of non-ß-oxidizable fatty acid analogues of the general formula (I):

Alkyl-X-CH_2COOR

wherein alkyl represents a saturated or unsaturated hydrocarbon group of from 8-22 carbon atoms, X represents O, S, SO, SO_2, and Se, and R represents hydrogen or C_1-C_4 alkyl, for the preparation of a pharmaceutical composition for the treatment and/or prevention of Syndrome-X conditions, with the exception of the Syndrome-X conditions claimed in European patent application 345.038 and International patent application WO 97/003663.

2. Use according to claim 1, for the preparation of a pharmaceutical composition for the treatment and/or for prevention of metabolic conditions of low levels of high density lipoprotein-cholesterol (HDL-C), and/or high levels of low density lipoprotein-cholesterol (LDL-C).

3. Use according to claim 1, for the preparation of a pharmaceutical composition for the treatment and/or prevention of raised triglycerides.

4. Use according to claim 1, for the preparation of a pharmaceutical composition for the treatment and/or prevention of glucose intolerance.

5. Use according to claim 1, for the preparation of a pharmaceutical composition for the treatment and/or prevention of non-insulin dependent diabetes mellitus (NIDDM).

6. Use according to claim 1, for the preparation of a pharmaceutical composition for the treatment and/or prevention of increased blood pressure.

7. Use according to claim 1, for the preparation of a pharmaceutical composition for the treatment and/or prevention of restinose.

8. Use according to claim 1, for the preparation of a pharmaceutical composition for the treatment and/or for prevention of abdominal obesity.

9. Use according to any of the preceding claims, wherein the compound of formula (I) is tetradecylthioacetic acid, or the compound of formula (I) is tetradecylselenocetic acid, or in the compound of formula I, X is Oxygen (O), Sulphur-I-oxide (SO) or Sulphurdioxide (SO_2).

10. A method for the treatment and/or for prevention of Syndrome-X conditions with the exception of the Syndrome-X conditions claimed in European patent application 345.038 and International patent application WO 97/003663, said method comprising administering to a mammal in need thereof, an effective amount of a non-ß-oxidizable fatty acid analogues of the general formula (I):

Alkyl-X-CH_2COOR

wherein alkyl represents a saturated or unsaturated hydrocarbon group of from 8-22 carbon atoms, X represents O, S, SO, SO_2, and Se, and R represents hydrogen or C_1-C_4 alkyl.

11. Method according to claim 8, for the preparation of a pharmaceutical composition for the treatment and/or for

prevention of metabolic conditions of low levels of high density lipoprotein-cholesterol (HDL-C), and/or high levels of low density lipoprotein-cholesterol (LDL-C).

12. Method according to claim 8, for the preparation of a pharmaceutical composition for the treatment and/or for prevention of raised triglycerides.

13. Method according to claim 8, for the preparation of a pharmaceutical composition for the treatment and/or for prevention of glucose intolerance.

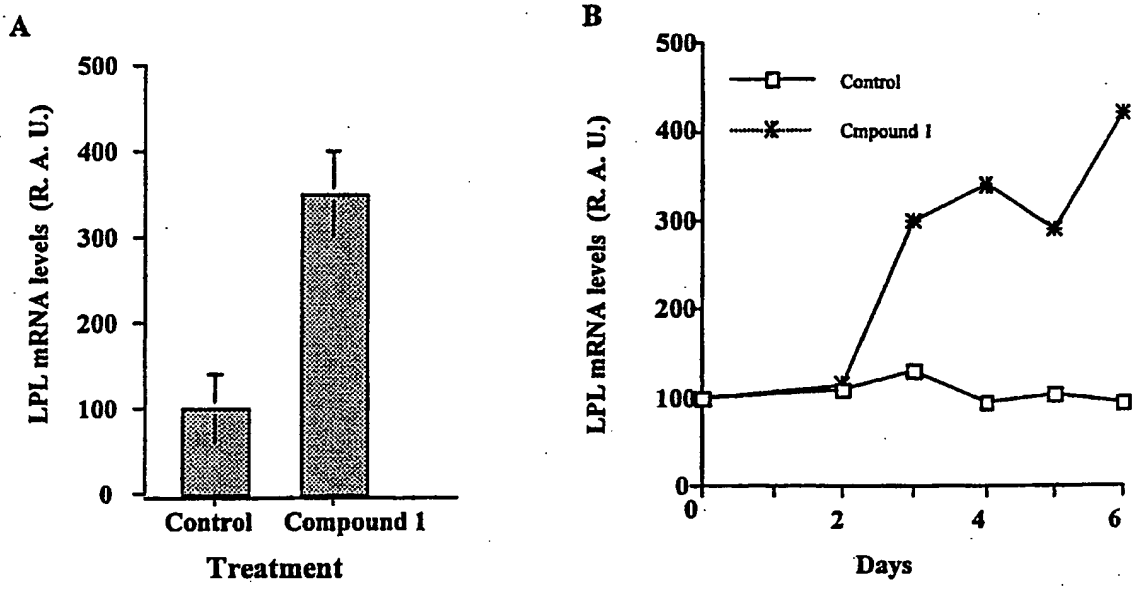
14. Method according to claim 1, for the preparation of a pharmaceutical composition for the treatment and/or for prevention of non-insulin dependent diabetes mellitus (NIDDM).

15. Method according to claim 1, for the preparation of a pharmaceutical composition for the treatment and/or for prevention of increased blood pressure.

16. Method according to claim 1, for the preparation of a pharmaceutical composition for the treatment and/or for prevention of restinose.

17. Method according to claim 1, for the preparation of a pharmaceutical composition for the treatment and/or for prevention of abdominal obesity.

18. Method according to any of the preceding claims, wherein the compound of formula (I) is tetradecylthioacetic acid, or the compound of formula (I) is tetradecylseleno-cetic acid, or the in the copound of formula I, X is Oxygen (O), Sulphur-I-oxide (SO) or Sulphurdioxide (SO_2).


A
500
400
300
200
100
0
LPL mRNA levels (R. A. U.)
Control
Compound 1
Treatment
B
500
400
300
200
100
0
LPL mRNA levels (R. A. U.)
Control
Cmpound 1
0
2
4
6
Days

INTERNATIONAL SEARCH REPORT

International application No.
PCT/NO 98/00143

A. CLASSIFICATION OF SUBJECT MATTER

IPC6: A61K 31/19, A61K 31/20
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAPLUS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 9703663 A1 (BERGE, ROLF), 6 February 1997 (06.02.97) --	1-18
X	EP 0345038 A2 (NORSK HYDRO A.S.), 6 December 1989 (06.12.89) --	1-18
X	STN International, File Caplus, Caplus accession no. 1997:308235, Forman, Barry Marc et al: "Hypolipidemic drugs, polyunsaturated fatty acids, and eicosanoids are ligands for peroxisome proliferator-activated receptors .alpha. and .delta." Proc. Natl. Acad. Sci. U. S. A. (1997), 94(9), 4312-4317 --	1-18

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" erlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
10 December 1998	11 -12- 1998
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Eva Johansson Telephone No. +46 8 782 25 00

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/NO 98/00143

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	STN International, File CAPLUS, CAPLUS accession no. 1996:57835, Froeyland, Livar et al: "Tetradecylthioacetic acid incorporated into very low density lipoprotein: changes in the fatty acid composition and reduced plasma lipids in cholesterol-fed hamsters", J. Lipid Res. (1995), 36(12), 2529-40	1-18
	--	
X	STN International, File CAPLUS, CAPLUS accession no. 1996:312821, Asiedu, Daniel K. et al: "Long-term effect of tetradecylthioacetic acid: a study on plasma lipid profile and fatty acid composition and oxidation in different rat organs", Biochim. Biophys. Acta (1996), 1300(2), 86-96	1-18
	--	
X	EP 0843972 A1 (N.V. NUTRICIA), 27 May 1998 (27.05.98)	1-18
	--	
X	STN International, File CAPLUS, CAPLUS accession no. 1997:363168, Aitman, Timothy J. et al: "Quantitative trait loci for cellular defects in glucose and fatty acid metabolism in hypertensive rats", Nat. Genet. (1997), 16(2), 197-201	1,10
	--	
X	STN International, File CAPLUS, CAPLUS accession no. 1994:76098, Schmidt, Erik Berg et al: "Omega-3 fatty acids, combined hyperlipemia and atherosclerosis with special reference to patiens with the atherogenic-syndrome", Omega-3 Fatty Acids: Metab. Biol. Eff. (1993), 211-16	1,10
	--	

INTERNATIONAL SEARCH REPORT

International application No.
PCT/NO 98/00143

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 10 and partly 18
because they relate to subject matter not required to be searched by this Authority, namely:
See PCT Rule 39.1(iv): Methods for treatment of the human or animal body by surgery or therapy, as well as diagnostic methods.

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [X] Claims Nos.: 11-18 see extra page
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/NO 98/00143

Claims 11-18 are not clear and concise, and does not comply with PCT Article 6, as each claim refers to a method and a use but fail to define the method.

The expression... "with the exception of the Syndrome-X conditions claimed in...." in claims 1 and 10 is not and clear and concise, and does not comply with PCT Article 6, as the kinds of conditions that are excluded from the claims are not stated.

INTERNATIONAL SEARCH REPORT

Information on patent family members

03/11/98

International application No.
PCT/NO 98/00143

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9703663 A1	06/02/97	AU 4272696 A	18/02/97
		CA 2226871 A	06/02/97
		EP 0840604 A	13/05/98
		NO 952796 D	00/00/00
EP 0345038 A2	06/12/89	SE 0345038 T3	
		CA 1329550 A	17/05/94
		DE 68910386 D,T	09/06/94
		DK 267689 A	03/12/89
		ES 2059749 T	16/11/94
		US 5093365 A	03/03/92
EP 0843972 A1	27/05/98	NO 975299 A	22/05/98